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(71) Applicant *(for all designated States except US)*: EMORY UNIVERSITY [US/US]; 1380 South Oxford Road, Atlanta, GA 30322 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PUSKAS, John, D. [US/US]; 854 Carlton Ridge, Atlanta, GA 30342 (US).

(74) Agents: PRATT, John, S. et al.; Kilpatrick Stockton LLP, Suite 2800, 1100 Peachtree Street, Atlanta, GA 30309–4530 (US).

(54) Title: PHARMACOLOGIC DRUG COMBINATION IN VAGAL–INDUCED ASYSTOLE

(57) Abstract

Controlled cessation of heart beat during coronary bypass surgery on a beating heart improves surgical technique, and is achieved typically by electrical stimulation of the vagus nerve and administration of a combination of drugs.

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PHARMACOLOGIC DRUG COMBINATION IN VAGAL-INDUCED ASYSTOLE

Background Of The Invention

Minimally invasive direct coronary artery bypass (MIDCAB) surgery is a substantially revolutionary development in surgery for allowing bypass surgery to be conducted on a beating heart. MIDCAB shows an undesirably higher rate of early graft failure than conventional coronary artery bypass procedures using cardiopulmonary bypass and cardioplegia. The technical difficulty of sewing the coronary artery anastomosis on a beating heart is likely an important factor in this difference in outcome between the two techniques. Controlled intermittent asystole (CIA) during brief intervals required for placing anastomotic sutures is suitable for improving the precision of MIDCAB anastomoses and reduce graft-failure while increasing ease of operation.

Cardiopulmonary bypass (CPB) and chemical arrest using cardioplegia solutions have provided surgeons with optimal operative conditions: hemodynamic control and cardiac quiescence. This optimal field has contributed to technical success in increasingly complex cardiac surgical operations. However, there has been recent interest in performing coronary artery bypass surgery without either cardiopulmonary bypass or cardioplegia. The quality of the distal anastomosis is a primary concern among cardiac surgeons who observe and perform CABG procedures unaided by cardioplegic arrest and cardiopulmonary bypass. Coronary artery bypass graft failure rates reported with "minimally invasive direct coronary artery bypass" (MIDCAB) range from 3.8 to 8.9%, while CABG on CPB has a reported anastomotic failure rate of 0.12%. This may reflect a difference in anastomotic precision between MIDCAB and CPB-aided CABG. Although the benefits of avoiding extracorporeal circulation in MIDCAB procedures are important, they do not outweigh the performance of an optimal CABG anastomosis.

The key difference in the anastomotic results between conventional CABG and MIDCAB is related to achieving elective asystole during construction of the distal anastomosis. Cardiac motion can be minimized during MIDCAB procedures via

pharmacologic bradycardia (adenosine, ß blockade) and mechanical stabilization using various devices. Although these techniques do improve operative conditions, they only approximate the advantages of elective asystole achieved with CPB and cardioplegia.

Applicants show that a state of controlled intermittent asystole (CIA) is produced off CPB, which provides a major advantage otherwise gained by cardioplegic arrest on CPB. In particular, CIA is achieved using unilateral vagus nerve stimulation coupled with pharmacologic suppression of electromechanical escape activity.

Applicants demonstrate that elective, controlled intermittent asystole is produced by vagus nerve stimulation before and after treatment with an acetylcholinesterase inhibitor, a ß-adrenergic receptor blocker, or a calcium channel blocker, or combination thereof.

Detailed Description of the Figures

Figure 1. Duration of asystole achieved during 60 second vagal stimulation. Lines connect the periods of asystole observed in the non-drug treated and drug treated states. Drug administration lengthened significantly the period of asystole.

Figure 2. Representative left ventricular and aortic pressure tracings during 60 second vagal stimulation in the non-drug treated (A) and drug treated states (B). Dark and open arrows mark the initiation and termination of the vagal impulse, respectively. Before drug treatment, a short pause followed by escape and bradycardia was observed during the 60 second impulse. After drug treatment, prolonged asystole occurred during the 60 second impulse with return of mechanical function after termination. lvp - left ventricular pressure; aop - aortic pressure.

Figure 3. Representative left ventricular and aortic pressure tracings during sequential 15 second vagal stimulations in the non-drug treated (A) and drug treated states (B). Dark and open arrows mark the initiation and termination of the vagal impulses, respectively. Before drug treatment, each 15 second stimulation produced a short pause followed by bradycardia, while after drug treatment, asystole lasted the

duration of each 15 second stimulation. lvp - left ventricular pressure; aop - aortic pressure.

Abbreviations and Definitions

CABG	Coronary artery bypass
CIA	Controlled intermittent asystole
CPG	Cardiopulmonary bypass
MIDCAB	Minimally invasive direct coronary artery bypass

Detailed Description Of The Invention

Increased acetylcholine activity by acetylcholinesterase inhibition and prevention of electromechanical escape activity by ß-adrenergic receptor and calcium channel blockade during vagal stimulation produces a marked potentiation of vagal-induced asystole and a means of achieving CIA. CIA achieved by pharmacologic potentiation of vagal-induced asystole is a suitable technique to facilitate MIDCAB operations. In particular, anastomoses and other complex suturing is facilitated during such controlled asystolic events, a readily appreciated advantage in surgery involving minimally invasive direct coronary artery bypass operations on a beating heart.

The present invention relates to a pharmaceutical composition, comprising an acetylcholinesterase inhibitor, or a β-adrenergic receptor blocker, or a calcium channel blocker, or combination thereof, said composition useful for minimally invasive direct coronary artery bypass heart surgery.

In one embodiment of the present invention, the composition is useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass surgery.

In another embodiment of the present invention, the composition is administered in combination with vagus nerve stimulation.

In another embodiment of the present invention, the pharmaceutical composition comprises an acetylcholinesterase inhibitor, a β-adrenergic receptor blocker, and a calcium channel blocker.

In another embodiment of the present invention, the acetylcholinesterase inhibitor is pyridostygmine bromide.

In another embodiment of the present invention, the β-adrenergic receptor blocker is propranolol hydrochloride.

In another embodiment of the present invention, the calcium channel blocker is verapamil bromide.

In another embodiment of the present invention, pharmaceutical composition comprises the acetylcholinesterase inhibitor pyridostigmine bromide, or the β-adrenergic receptor blocker propranolol hydrochloride, or the calcium channel blocker verapamil bromide, or combination thereof, said composition useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass heart surgery.

In another embodiment of the present invention, the pharmaceutical composition comprises the acelylcholinesterase inhibitor pyridostigmine bromide, the β-adrenergic receptor blocker propranolol hydrochloride, and the calcium channel blocker verapamil bromide, said composition useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass heart surgery.

The principal challenge of MIDCAB has been to recreate the advantageous operative conditions of a quiescent, bloodless operative field provided during conventional CABG with CPB and cardioplegic arrest. A variety of pharmacologic manipulations and mechanical stabilizing techniques assist in performing CABG off pump. These interventions to date minimize, but do not eliminate, cardiac motion. The concept that a state of controlled intermittent asystole improves the conditions for construction of distal coronary artery bypass anastomosis in non-CPB assisted cases was demonstrated by applicants. CIA is defined as operator-initiated and controlled intervals of mechanical cardiac standstill that coincide with placement of sutures in the anastomosis, after which normal cardiac rhythm and hemodynamics are restored while preparations are made for the next successive stitch. These experiments indicated that the bradycardia known to be produced by vagus nerve stimulation is suitable for the functional electromechanical "on-off switch" by inhibition of acetylcholinesterase and blockade of ß-adrenergic receptors and calcium channels.

The chronotropic effects of vagal nerve stimulation have been well described and typically produce an initial pause followed by a "vagal escape" beat and sustained bradycardia during continuous optimal stimulation of the vagus nerve. Cardiac responses to a 60 second vagal stimulation without adjunctive therapy achieved an average pause of 1.6 seconds terminated by vagal escape beats with a 19% reduction in heart rate. Vagus nerve stimulation alone did not produce a controlled period of asystole desired for CIA. In contrast, a triple pharmacologic regimen of e.g., pyridostigmine, propranolol and verapamil inhibited vagal escape, and allowed sustained periods of asystole lasting up to 60 seconds and sequential asystoles of 15 seconds each. Segmental asystoles had no significant homodynamic consequences.

It is apparent that suppression of the electromechanical escape during vagal stimulation is necessary to produce a sufficient interval of asystole to allow during which a single stitch may be reliably placed during construction of a distal CABG anastomosis. The negative chronotropic effects of vagal stimulation are produced by acetylcholine release. Acetylcholine activity may be enhanced by inhibition of acetylcholinesterase activity by agents such as pyridostigmine. Additionally, it is known that calcium channel blockade by e.g. verapamil potentiates the negative chronotropic effect of vagus nerve stimulation. Another component in electromechanical escape may be related to increased catecholamine activity in the sympathetic nervous system, triggered by hypotension. Catecholamines increase the rate of diastolic depolarization and decrease the threshold potential. ß-adrenergic receptor blockade via e.g. propranolol reduces the effects of catecholamine activity and facilitates suppression of electromechanical escape.

Administration of this combination therapy produced a significant reduction in heart rate and maximum developed ventricular pressure along with an increase in left ventricular end-diastolic pressure, but did not alter mean arterial pressure. There was no apparent fatigue of this pharmacologic effect after sequential stimulations. The animals appeared to tolerate this pharmacologic regimen without other adverse hemodynamic side effects such as acidosis.

The short-term hemodynamic effects of a single prolonged stimulation were found to be substantially insignificant. Likewise the metabolic consequences as

detected by pH and changes in base deficit were insignificant. However, the neurologic consequences of prolonged asystole or multiple sequential brief periods of asystole are an important concern. Asystolic intervals would produce cerebral hypoperfusion similar in duration to that which occurs during placement and testing of automatic implantable cardioverter-defribrilator (AICD) devices. Careful electroencephalographic (EEG) studies have documented reversible EEG changes of ischemia at 7.5 seconds after fibrilatory arrest, however neurologic and neuropsychometric evaluation has demonstrated no new deficits after AICD implantation in patients undergoing asystolic intervals.

The pharmacologic regimen used in this investigation sustained the period of vagal-induced asystole for about sixty minutes. This interval would allow more than sufficient time for construction of a distal CABG anastomosis. Animals followed for two hours after administration of drugs displayed responses to vagal stimulation similar to those in the non-drug treated state, confirming reversibility of the drug effects. No animal displayed complete atrioventricular nodal blockade, a potential problem when ß-blockers and calcium channel blockers are combined.

An untoward effect of the pharmacologic regimen which requires consideration before clinical application is vagal-induced secretions. All animals displayed significant salivation after initiation of vagal stimulation. However, there were no problems with oxygenation and ventilation due to tracheobronchial secretions in these experiments. Vagal-induced oripharyngeal and tracheobronchial secretions are pertinent in the clinical setting. Additionally, the effects on recurrent laryngeal nerve function require consideration.

Evidence suggests that the long-term effects of this regimen on the vagus nerve are not harmful. Chronic vagus nerve stimulation has been utilized as therapy for intractable seizure disorders without apparent nerve injury or impaired function. Applicants have shown that vagal-mediated chronotropic control at two hours after completion of the experimental protocol was similar to the non-drug treated state.

In summary, controlled intermittent asystole can be achieved by potentiation of vagal-induced asystole via a pharmacologic combination of e.g., propranolol and verapamil for suppression of electromechanical escape and e.g., pyridostigmine for

acetylcholinesterase inhibition. Asystole can be reproducibly achieved for prolonged intervals and for shorter multiple sequential intervals using this technique.

Nerve Stimulation

To achieve consistent asystole, applicants have found that nerve stimulation of the right vagus nerve before or after treatment with the pharmacological combinations of the present invention is preferred.

Electrical stimulation is carried out on the right vagus nerve, preferably at a site on the neck. Other suitable locations for vagus nerve stimulation include, but are not limited to, stimulation in the chest after sternotomy, stimulation with an esophageal probe or in the internal jugular vein. The nerve stimulator is typically a Grass wire with a single point of contact, but other suitable stimulators include a pair of pacing wires placed about 1 cm apart to allow prodromic stimulation. A single continuous impulse is applied of between about 5 seconds to about 90 seconds, preferably between about 5 seconds and about 15 seconds to allow single stitch during surgery. Impulse parameters can readily be varied, e.g., a frequency range of between about 1Hz and about 500Hz, preferably between about 20 Hz to about 80Hz, more preferably about 40 Hz, with an amplitude between about 1 to about 40 volts.

Pharmacologic Potentiation

The acetylcholinesterase inhibitor is also known as a cholinesterase inhibitor. Suitable acetylcholinesterase inhibitors include, but are not limited to tacrine hydrochloride, pyridostigmine bromide, neostigmine methylsulfate, and edrophonium chloride. One preferred acetylcholinesterase inhibitor is pyridostigmine bromide. Acetylcholinesterase inhibitors are administered in a dosage range between about 0.01 mg/kg and about 100 mg/kg, preferably between about 0.1 mg/kg and about 2.0 mg/kg, more preferably about 0.5 mg/kg.

The beta-adrenergic receptor blocker is also known as a beta-adrenergic blocking agent. Suitable beta-adrenergic receptor blockers include, but are not limited to, sotalol HCl, timolol maleate, esmolol hydrochloride, carteolol hydrochloride, propranolol hydrochloride, betaxolol hydrochloride, penbutolol sulfate, metoprolol

tartrate, acetbutolol hydrochloride, the combination of atenolol and chlorthalidone, metoprolol succinate, pindolol, and bisoprolol fumarate. One preferred beta-adrenergic receptor blocker is propranolol hydrochloride. Beta-adrenergic receptor blockers are administered in a dosage range between about 0.01 μg/kg and about 100 mg/kg, preferably between about 0.2 μg/kg and about 2.0 mg/kg, more preferably about 80 μg/kg.

Suitable calcium channel blockers include, but are not limited to, nifedipine, nicardipine hydrochloride, diltiazem HCl, isradipine, verapamil hydrochloride, nimodinpine, amlodipine besylate, felodipine, bepridil hydrochloride, and nisoldipine. One prefererred calcium channel blocker is verapamil hydrochloride. Calcium channel blockers are administered in a dosage range of between about 1μg/kg to about 1000 μg/kg, preferably between about 10μg/kg and about 200μg/kg, more preferably about 50 μg/kg.

It will be understood that other dosage combinations may be effective. The appropriate dosage is determined by the age, weight, sex, health status of the patient, and may vary with a variety of other factors according to conventional clinical practice.

EXAMPLE 1

Experimental Preparation

The sheep in the examples of the present invention received humane care in compliance with "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 80-23, revised 1985). The experimental protocol was approved by the Institutional Animal Care and Use Committee of Emory University.

Seven sheep weighing 45 to 44 kg were premedicated with xylazine (0.1mg/kg) and atropine (0.2 mg/kg) 30 minutes prior to induction of anesthesia with intravenous thiopental (2.2 mg/kg) and lidocaine (2.2 mg/kg). The animals were endotracheally intubated and placed on a volume ventilator with isoflurane for maintenance of

anesthesia. Limb leads and precordial lead were placed for electrocardiographic monitoring. The right femoral artery was cannulated for arterial pressure and arterial blood gas monitoring. Tidal volume was adjusted to 10 cc/kg and a rate of 12 breaths per minute, with adjustments made to maintain pH at 7.35-7.45, pO2 greater than 100mm Hg, and pCO2 between 35-45 mmHg.

A right cervical incision was performed, the vagus nerve was carefully isolated and a nerve stimulation probe (Harvard Apparatus, South Natick, MA) was placed on the nerve. A median sternotomy was made to expose the heart. A high-fidelity solid-state micromanometer (Millar Inc., Houston, TX) was secured in the ascending aorta for aortic blood pressure monitoring. An additional micromanometer was introduced into the left ventricle through the apex for left ventricular pressure monitoring.

EXAMPLE 2

Experimental Protocol

Each animal underwent vagal stimulation before and after drug administration. The pharmacologic regimen consisted of pyridostigmine (0.5 mg/kg) for acetylcholinesterase inhibition, propranolol (80 µg/kg) for ß-adrenergic receptor blockade, and verapamil (50 µg/kg) for calcium channel blockade. Vagal stimulation was performed with a nerve stimulator (Grass Instrument Co., Quincy, MA) in the monopolar mode at a frequency of 40 Hz, an impulse duration of 0.4 msec, and an amplitude of 2-6 volts. Vagal stimulations were delivered in two regiments: 1) continuous 60 second impulse and 2) sequential 15 second impulses. The continuous 60 second stimulation was designed to determine the longevity of vagal-induced asystole and the physiologic effects of prolonged vagal-induced hypotension. Sequential 15 second vagal stimulations were performed to simulate the suturing intervals required for graft anastomoses and to determine whether cardiac fatigue, electromechanical escape, and physiologic effects occurred under these practical conditions.

EXAMPLE 3

Data Acquisition and Analysis

Electrocardiographic and hemodynamic data were gathered via an analog-to-digital conversion board (Data Translation, Inc., Marlboro, MA) and processed, stored, and analyzed via a microprocessor personal 486 computer (Compaq Computer Corp., Houston, TX) using interactive proprietary software (Spectrum™, Triton Technology, San Diego, CA). The system was configured to collect 4 channels of physiologic data at a frequency of 50 Hz (sufficient for slow-wave waveforms and mean pressure data) over a 200 second period that encompassed the 60 second stimulation or the sequential 15 second train of stimulations. The software allowed subsequent videographic display and analysis of the hemodynamic data.

EXAMPLE 4

Results

Before drug administration, vagal stimulation for 60 seconds produced a brief pause in electromechanical activity (1.6 ± 0.9 seconds) followed by vagal escape and resumption of sinus rhythm with a reduction in heart rate by 19.4 ± 11.9% compared to pre-stimulation heart rate. Similarly, sequential 15 second vagal stimulation performed to stimulate the suturing intervals required for CABG anastomoses produced a short pause (1.1 ± 0.4 seconds) followed by vagal escape and sinus rhythm with a reduction in heart rate of 37 ± 6%.

Administration of the pharmacologic regimen (propranolol, verapamil, pyridostigmine) reduced the heart rate and increased the left ventricular end diastolic pressure, but did not affect the mean arterial pressure or maximum dP/dt as shown in Table 1.

Table 1. Hemodynamics before and after drug treatment

	Before drugs (mean ± SEM)	After drugs (mean ± SEM)	*p* value (paired *t* test)
Heart rate (bpm)	114 ± 4	87 ± 4	0.002
MAP (mm Hg)	84 ± 5	84 ± 5	NS
dP/dt max (mm Hg/sec)	3286 ± 232	2847 ± 140	NS
LVEDP (mm HG)	3.9 ± 0.5	7.3 ± 0.9	0.005

bpm - beats per minute; dP/dt max - maximum developed left ventricular pressure; LVEDP - left ventricular end diastolic pressure; MAP - mean aortic pressure; NS - not significant; SEM - standard error of the mean; sec - seconds.

After drug administration, 60 second vagal stimulation produced asystole averaging 52 ± 5.6 seconds. The individual responses of the animals before and after drug administration are shown in Figure 1. Five animals achieved asystole for greater than 50 seconds. One individual displayed no asystolic responses either before or after drug treatment; incremental doses of drugs did not improve responsiveness in this animal. This animal was termed a non-responder and was excluded from further analysis. The effects of 60 second vagal stimulation before and after drug treatment in responsive animals are contrasted by representative left ventricular and aortic pressure tracings are shown for a representative experiment in Figure 2. Before drug regimen treated, vagal stimulation produced no appreciable change in cardiac rhythm or hemodynamics. In contrast, the triple drug regimen facilitated a consistent asystole and circulatory arrest until the stimulus was withdrawn, after which hemodynamics were rapidly restored to pre-stimulation values. The prolonged asystole and circulatory arrest produced no significant differences in the hemodynamic parameters measured before and after drug-aided 60 second vagal stimulation (Table 2).

Table 2. Hemodynamics pre- and post-asystole produced by 60 second stimulation after drug treatment

	Pre-asystole (mean ± SEM)	Post-asystole (mean ± SEM)	*p* value (paired *t* test)
Heart rate (bpm)	91 ± 8	87 ± 7	NS
MAP (mm Hg)	86 ± 6	92 ± 6	NS
dP/dt max (mm Hg/sec)	3032 ± 182	3223 ± 212	NS
LVEDP (mm Hg)	5.8 ± 1.0	6.0 ± 0.8	NS

bpm - beats per minute; dP/dt max - maximum developed left ventricular pressure; LVEDP - left ventricular end diastolic pressure; MAP - mean aortic pressure; NS - not significant; SEM - standard error of the mean; sec - seconds.

Likewise there was no difference in the parameters measured by arterial blood gases at one and five minutes after the 60 second stimulation compared to pre-stimulation values (Table 3).

Table 3. Arterial blood gas data pre-, 1 minute post-, and 5 minutes post-systole produced by 60 second stimulation after drug treatment

	Pre-asystole	Post-asystole		p *p* value
		1 minute	5 minutes	
	(mean ± SEM)	(mean ± SEM)	(mean ± SEM)	(ANOVA)
pH	7.42 ± 0.03	7.40 ± 0.03	7.42 ± 0.03	NS
PCO_2 (mm Hg)	41 ± 4	42 ± 4	40 ± 4	NS
PO_2 (mm Hg)	377 ± 87	380 ± 75	390 ± 83	NS
HCO_3 (mEq/L)	26 ± 1	26 ± 1	26 ± 1	NS
Base excess (mEq/L)	1.2 ± 0.7	1.0 ± 0.4	1.3 ± 0.5	NS

ANOVA - one-way analysis of variance with repeated measures; NS - not significant; SEM - standard error of the mean.

Five to six sequential 15 second vagal stimulations in the drug treated state produced consistent and stable asystole (Figure 3). Three of the six animals had a single escape beat during one of the 15 second stimulations. The other three displayed complete asystole during each of the 15 second stimulations. A sustained cardiac rhythm began an average of 5.3 ± 1.8 seconds after termination of each 15 second impulse during which interval a single beat was often observed immediately after withdrawal of stimulation.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, and modifications, as come within the scope of the following claims and its equivalents.

What Is Claimed Is:

1. A pharmaceutical composition, comprising an acetylcholinesterase inhibitor, or a β-adrenergic receptor blocker, or a calcium channel blocker, or combination thereof, said composition useful for minimally invasive direct coronary artery bypass heart surgery.
2. The pharmaceutical composition of claim 1, useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass surgery.
3. The composition of claim 1, wherein said composition is administered in combination with vagus nerve stimulation.
4. A pharmaceutical composition of any of claims 1-3, comprising an acetylcholinesterase inhibitor, a β-adrenergic receptor blocker, and a calcium channel blocker.
5. The composition of any of claims 1-3, wherein the acetylcholinesterase inhibitor is pyridostygmine bromide.
6. The composition of claim 4, wherein the acetylcholinesterase inhibitor is pyridostygmine bromide.
7. The composition of any of claims 1-3, wherein the β-adrenergic receptor blocker is propranolol hydrochloride.
8. The composition of claim 4, wherein the β-adrenergic receptor blocker is propranolol hydrochoride.
9. The composition of any of claims 1-3, wherein the calcium channel blocker is verapamil bromide.
10. The composition of claim 4, wherein the calcium channel blocker is verapamil bromide.
11. A pharmaceutical composition, comprising the acetylcholinesterase inhibitor pyridostigmine bromide, or the β-adrenergic receptor blocker propranolol hydrochloride, or the calcium channel blocker verapamil bromide, or combination thereof, said composition useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass heart surgery.
12. A pharmaceutical composition, comprising the acelylcholinesterase inhibitor pyridostigmine bromide, the β-adrenergic receptor blocker propranolol

hydrochloride, and the calcium channel blocker verapamil bromide, said composition useful for controlled intermittent asystole in minimally invasive direct coronary artery bypass heart surgery.

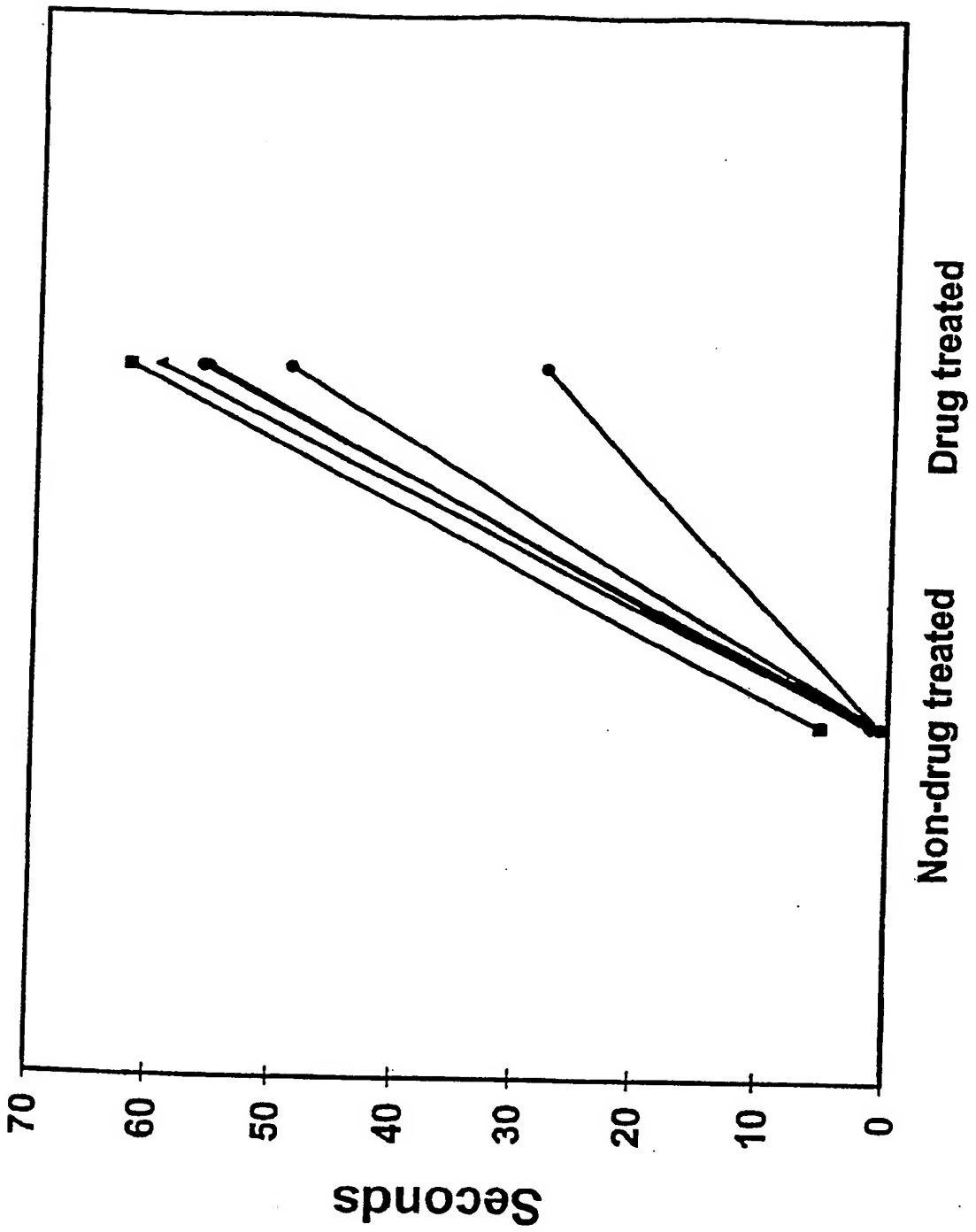

FIG. 1

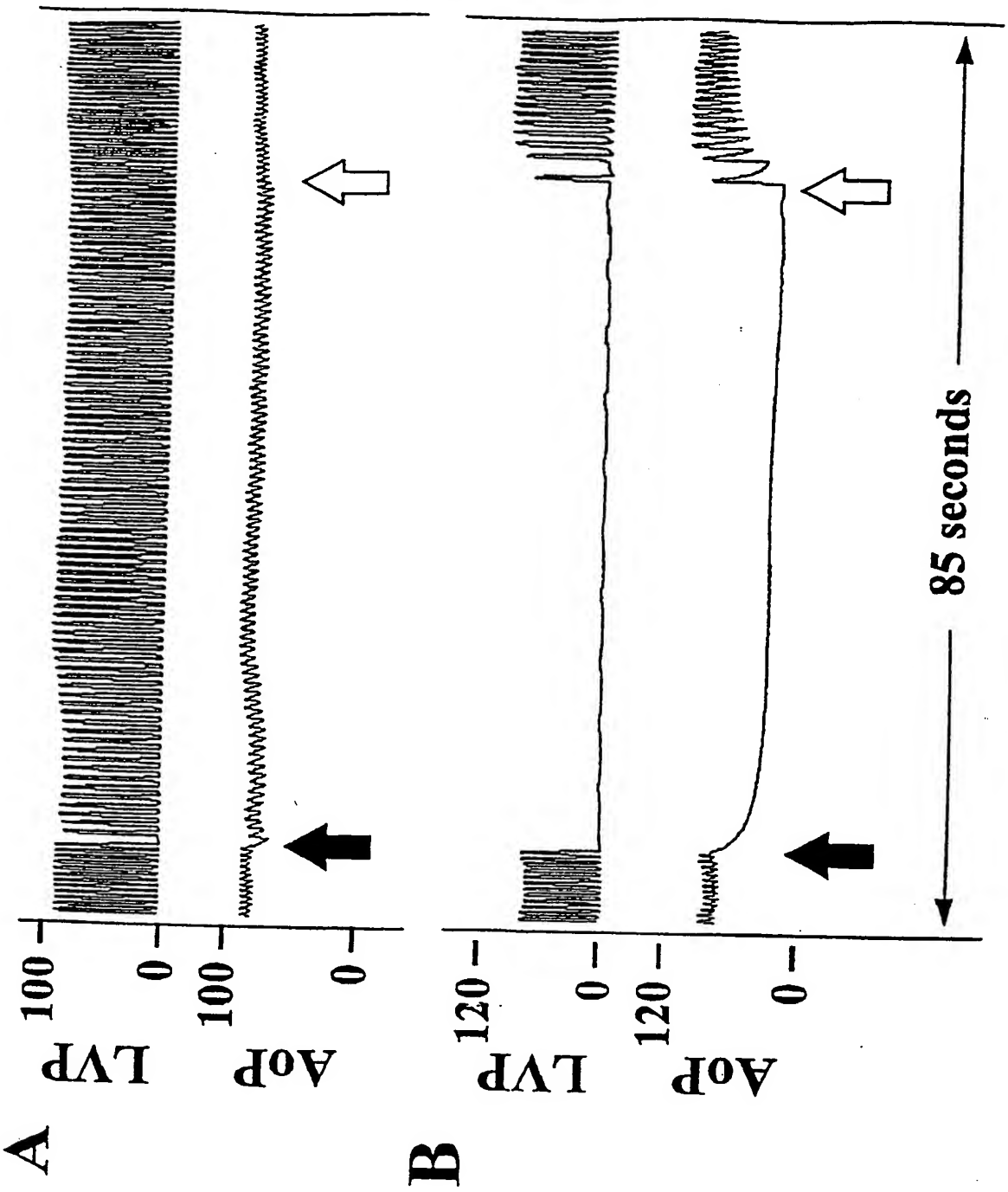

FIG. 2

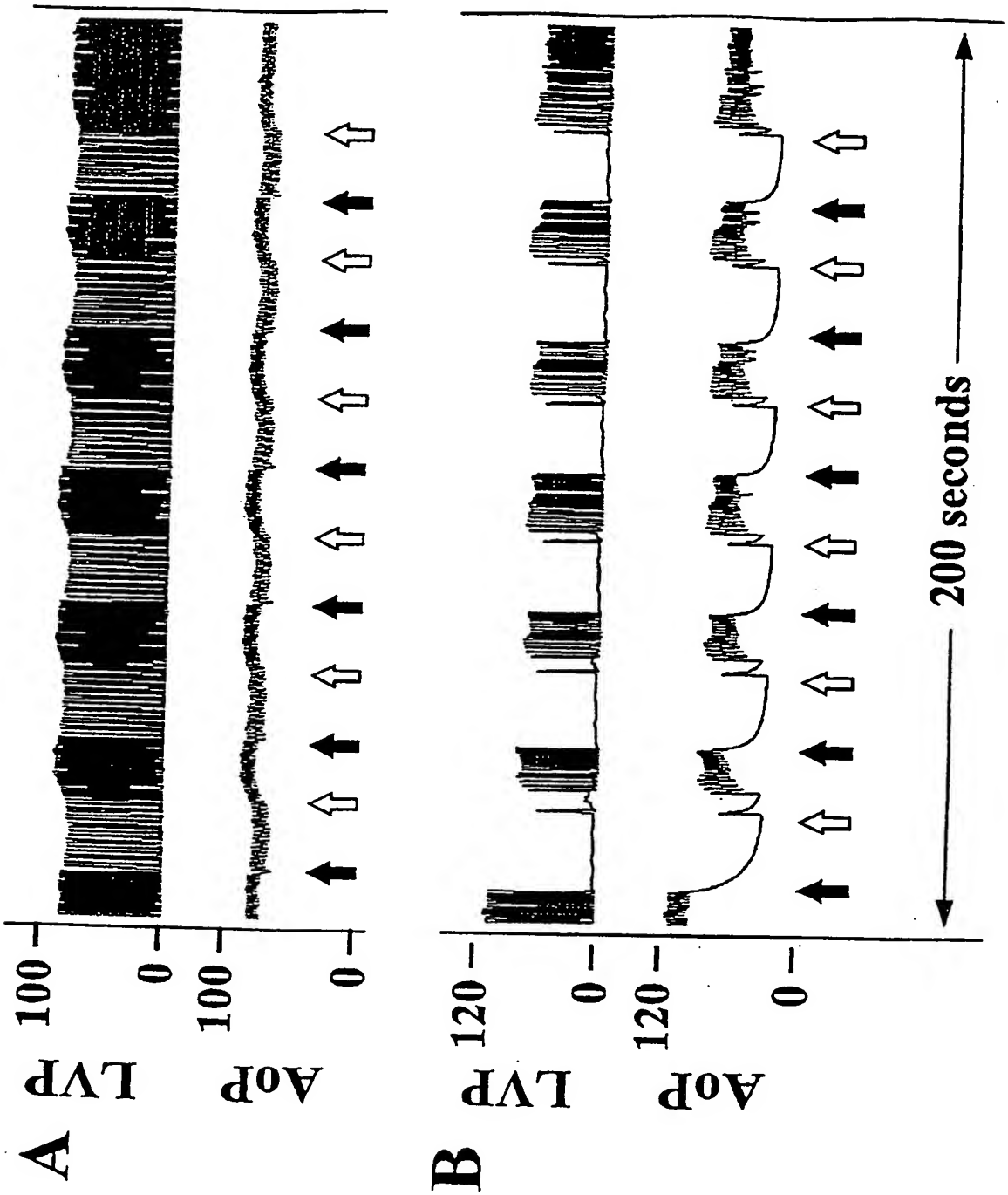

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16411

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/135
US CL : 514/652
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/652

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,952,586 A (MORRIS ET AL.) 28 August 1990, see the entire document.	1-12
Y	US 4,931,464 A (GROVER ET AL.) June 5, 1990, see the entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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10 SEPTEMBER 1998	16 OCT 1998

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